What Data Do We Have Already and Where Are the Gaps?

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Food Allergy Research & Resource Program
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ILSI-Europe Workshop
Food Allergy: From Thresholds to Action Levels
Reading U.K.; Sept. 13-14, 2012
Existing Data

- VITAL data on dose-distribution of individual thresholds for 11 allergenic foods
- Recommended Reference Doses for these foods
- Statistical modeling approaches
- Interval Censoring Survival Analysis as a means to work with NOAELs and LOAELs
- Quantitative Risk Assessment approach
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### Number of Threshold Data Points Gleaned From Publications and Unpublished Clinical Records.

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Total No. with Objective Symptoms</th>
<th>Right Censored*</th>
<th>Left Censored**</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>750</td>
<td>132</td>
<td>30</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Milk</td>
<td>351</td>
<td>19</td>
<td>59</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Egg</td>
<td>206</td>
<td>33</td>
<td>24</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>202</td>
<td>67</td>
<td>4</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Soybean</td>
<td>80</td>
<td>28</td>
<td>6</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Wheat</td>
<td>40</td>
<td>1</td>
<td>5</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Cashew</td>
<td>31</td>
<td>16</td>
<td>1</td>
<td>Children</td>
</tr>
<tr>
<td>Mustard</td>
<td>33</td>
<td>10</td>
<td>2</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Lupin</td>
<td>24</td>
<td>7</td>
<td>2</td>
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</tr>
<tr>
<td>Sesame</td>
<td>21</td>
<td>1</td>
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</tr>
<tr>
<td>Shrimp</td>
<td>48</td>
<td>26</td>
<td>0</td>
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</tr>
<tr>
<td>Celery</td>
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</tbody>
</table>

*Number of right-censored subjects (NOAEL = highest challenge dose; LOAEL set to infinity).

**Number of left-censored subjects (NOAEL set at zero; LOAEL = lowest challenge dose).
Source of Existing Data

- Blinded, controlled oral challenges conducted in allergy clinics on food-allergic patients
- Various clinical protocols: nature of allergen material; nature of food matrix; degree of processing; time between challenges; discrete vs. cumulative doses; nature of response
Clinic Selection

- Clinics doing DBPCFC
- Low-dose oral challenges
- Published studies preferred
- Diagnostic challenges
- Immunotherapy trials
- Threshold studies
Patient Selection

- Positive response to DBPCFC
- Sometimes convincing history of reaction to food
- Referral clinics often involved so possibly biased toward more sensitive patients
- No exclusion of severe reactors in some clinics
- Immunotherapy and threshold trials may bias toward more sensitive patients
Patient Selection

- Positive response to DBPCFC
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Table 4. ED$_{10}$ doses for peanut protein according to history of severity (Based on the log-normal probability distribution model).

<table>
<thead>
<tr>
<th>Severity Grade (by history)</th>
<th>Total No. of Peanut Allergic Individuals</th>
<th>ED$_{10}$ (mg protein)</th>
<th>95% CI (mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe$^1$</td>
<td>40</td>
<td>2.6</td>
<td>1.2, 5.7</td>
</tr>
<tr>
<td>Non-Severe$^2$</td>
<td>123</td>
<td>2.6</td>
<td>1.6, 4.0</td>
</tr>
<tr>
<td>No Prior History$^3$</td>
<td>123</td>
<td>6.8</td>
<td>4.4, 10.5</td>
</tr>
</tbody>
</table>

$^1$Severe reactions include three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension.

$^2$Non-severe reactions include one or two organ systems, abdominal pain, rhinoconjunctivitis, urticaria, eczema, non-laryngeal angioedema, and/or mild asthma (peak flow rate <80%)

$^3$History of prior allergic reactions and severity of reactions were not available. These individuals were identified as being sensitized to peanut by means of diagnostic tests.

All values reported in mg peanut protein

Conclusion: no evidence of relationship between prior severity and population sensitivity
Patient Selection

- Positive response to DBPCFC
- Sometimes convincing history of reaction to food
- Referral clinics often involved so possibly biased toward more sensitive patients
- No exclusion of severe reactors in some clinics
- Immunotherapy and threshold trials may bias toward more sensitive patients
**FARRP Peanut Threshold Analysis: Additional Clinical Data**

ED$_{10}$ and ED$_{05}$ Doses for Peanut Protein as Assessed by the Log-Normal Probability Distribution Models

<table>
<thead>
<tr>
<th>Source</th>
<th>Total No. of Peanut Allergic Individuals</th>
<th>ED$_{10}$ (mg protein)</th>
<th>95% CI (mg protein)</th>
<th>ED$_{05}$ (mg protein)</th>
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<tbody>
<tr>
<td>FARRP 450 Dataset</td>
<td>450</td>
<td>3.1</td>
<td>2.3, 4.2</td>
<td>1.3</td>
<td>0.9, 1.9</td>
</tr>
<tr>
<td>Immunotherapy Studies</td>
<td>64</td>
<td>0.7</td>
<td>0.2, 2.1</td>
<td>0.3</td>
<td>0.1, 0.9</td>
</tr>
<tr>
<td>Combined</td>
<td>750*</td>
<td>3.8</td>
<td>3.0, 5.0</td>
<td>1.5</td>
<td>1.1, 2.1</td>
</tr>
</tbody>
</table>

All values reported in mg of peanut protein; *436 patients from other clinical sources (most diagnostic challenge)

**Conclusion:** Immunotherapy studies appear biased toward more sensitive subjects
Resolution of Protocol Differences

- Allergenic material normalized on protein basis
  (peanut – 25% protein; peanut flour – 50% protein)
- Food matrix differences ignored
- Degree of processing probably makes a difference
  in some cases but inadequate data exist so all
  considered as equal
- Time between challenges ignored
- Discrete vs. cumulative compared but no difference
- Objective symptoms only
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**Number of left-censored subjects (NOAEL set at zero; LOAEL = lowest challenge dose).
Existing Data

- Large numbers of subjects for peanut, milk, egg, and hazelnut
- But, relatively few adults for milk and egg
- Lesser number of subjects for soy, wheat, cashew, mustard, lupine, sesame seed, shrimp, celery and fish
- No data for adults with cashew
- No data for children with shrimp
Data Gaps

- No data exist on other tree nuts (walnuts, almonds, etc.) or molluscan shellfish
- Data on celery and fish were inadequate to allow modeling
- Would be nice to have more data for all but peanut; with milk and egg, only more adults needed
- How many people are excluded from challenge on account of prior severe reaction?
Future Research

- One shot experiment
- Comparison of effects of processing on certain allergenic foods (e.g. eggs and soy)
- Differences among species (fish, crustacean shellfish, molluscan shellfish)
- Children vs. adults
Existing Data

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# ILSI-Europe Scientific Expert Panel Recommendations

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<thead>
<tr>
<th>Allergen</th>
<th>mg Protein Level</th>
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<tbody>
<tr>
<td>Peanut</td>
<td>0.2</td>
</tr>
<tr>
<td>Milk</td>
<td>0.1</td>
</tr>
<tr>
<td>Egg</td>
<td>0.03</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>0.1</td>
</tr>
<tr>
<td>Soy</td>
<td>1.0</td>
</tr>
<tr>
<td>Wheat</td>
<td>1.0</td>
</tr>
<tr>
<td>Cashew</td>
<td>2.0 (provisional)</td>
</tr>
<tr>
<td>Mustard</td>
<td>0.05</td>
</tr>
<tr>
<td>Lupin</td>
<td>4.0</td>
</tr>
<tr>
<td>Sesame</td>
<td>0.2</td>
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<td>10.0</td>
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Recommended Reference Doses

- Based upon ED01 or 95% lower confidence interval of ED05 (dependent on number of data points)
- No additional uncertainty factors were applied
- At least 95-99% of allergic consumers protected by these Reference Doses
Existing Data

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PEANUT
Log-Normal Population Distribution (expressed as mg peanut protein)
Log-Logistic Population Distribution (expressed as mg peanut protein)
Weibull Population Distribution (expressed as mg peanut protein)
Peanut Threshold Population Distributions (expressed as mg peanut protein)
Log-Normal Population Distribution (expressed as mg soy protein)
Log-Logistic Population Distribution (expressed as mg soy protein)
Weibull Population Distribution (expressed as mg soy protein)
Soy Flour Threshold Population Distributions
(expressed as mg soy protein)
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Interval-Censoring Survival Analysis

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>10mg</th>
<th>50mg</th>
<th>150mg</th>
<th>500mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 3</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Left-censored
Interval-censored
Right Censored

No Reaction
Reaction Interval

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ICSA and Existing Data

- Ideal situation if all of the clinical data were interval censored
- Narrower intervals are better but not so critical
- Can handle many different intervals (multiple protocols)
- Left censored has larger effect than right censored so cannot easily use data from protocols with high % of left censored
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QRA Diagram

NHANES Survey → Consumption Quantity (g)

Product analyses → Levels (ppm)

Clinical studies → Thresholds (mg)

Allergen intake (mg)

No Allergic Reaction → Allergic Reaction

Adapted from Geert Houben, TNO
Gaps with QRA

- Threshold distributions are reasonably solid but more data is always better
- Need consumption distributions from more countries; USA okay; EU – many missing
- Need consumption distributions for food-allergic segment; same as others?
- Concentration distribution based on analytical data or calculations – reasonably strong but could improve
Gaps with QRA

- Particulate contamination is problematic and a common basis for precautionary labeling.
- But do the particles exceed the Reference Doses in all cases?
- QRA predicts number of reactions but does not predict number/likelihood of severe reactions.
- Need to have better understanding of distribution of severity at a given dose – the one-shot study.
Overall Conclusions

- Sufficiently abundant data exist to generate reasonably reliable dose distributions
- Existing data are also of sufficiently good quality for this purpose
- Human subjects; vulnerable segment
- Some of the most sensitive subjects have been included especially IT trial patients for some foods
- Exclusion of those with history of severe reactions won’t have much effect on distributions
- Can estimate ED10, ED05, and sometimes ED01
Overall Conclusions

- Reasonably robust Reference Doses can be established based upon the dose distributions
- Reference Doses selected conservatively due to emphasis on highly sensitive patients
- Reference Doses could be adopted as benchmarks for allergen management and precautionary labeling
- The alternative is to continue with the status quo which is not serving the needs of any of the stakeholders very well
**Overall Conclusions**

- Did this ILSI-Europe Task Force select the right Reference Doses?
- Will these Reference Doses be sufficiently protective?
- Can the food industry achieve this level of consumer protection?